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Respiratory Medicine (2013) 107, 292–297

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The efficacy of rifabutin for rifabutin-susceptible, multidrug-resistant tuberculosis

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Received 3 April 2012; accepted 9 October 2012
Available online 28 November 2012

KEYWORDS
Rifabutin;
Multidrug-resistant tuberculosis;
Efficacy

Summary
Objective: We investigated the efficacy of rifabutin (RFB)-containing regimens for the treatment of RFB-susceptible, multidrug-resistant tuberculosis (MDR-TB).
Methods: From 146 patients diagnosed with MDR-TB between January 2006 and December 2009 at Asan Medical Center in South Korea, 31 patients (21.2%) were found to have RFB-susceptible MDR-TB. Of these 31 patients, 14 patients who had been treated with RFB for more than one month were included. Forty-two patients with RFB-resistant MDR-TB were selected as a control group, and the outcomes of both groups were retrospectively compared.
Results: Of 14 patients with RFB-susceptible MDR-TB, the mean age was 44.4 years and the proportion of extensively drug-resistant TB (XDR-TB) was 35.7% (5/14). Baseline characteristics and the drug resistance pattern (except RFB) did not differ between the two groups. Treatment success was achieved in 12 (85.7%) patients in the RFB group: cure in 10 (71.4%) and treatment completion in two (14.3%). The treatment success rate was 52.4% (22/42) in the control group ($p = 0.032$). Treatment failure was more common in patients of the control group (40.5% vs. 14.3%; $p = 0.106$).
Conclusions: RFB is useful as an additional drug in the treatment of MDR-TB in patients with RFB-susceptible MDR-TB.
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http://dx.doi.org/10.1016/j.rmed.2012.10.021

Introduction

Multidrug-resistant tuberculosis (MDR-TB) affects people in all regions of the world and remains a serious threat to public health.[1] In addition, the appearance of extensively drug-resistant TB (XDR-TB), a subset of MDR-TB, has complicated both the treatment and control of the disease.[2] In South Korea, an intermediate TB-burden country, 2.7% of patients newly diagnosed with TB and 14% of patients with a history of previous TB treatment were found to have MDR-TB in 2004.[3] Additionally, XDR-TB is estimated to occur in approximately 5—10% of the patients with MDR-TB.[4] In South Korea, the overall treatment success rate has been reported to be 45.3% among 1407 patients with MDR-TB and only 29.3% among patients diagnosed with XDR-TB.[5] Despite the global effort to control MDR-TB, few new drugs have been developed to treat it since 1970.

Rifabutin (RFB) is a first-line anti-TB drug which is reserved for patients with drug-susceptible TB and who are taking medications incompatible with rifampicin (RIF), such as antiretroviral drugs.[6,7] Although RFB may have comparable rates of cure and relapse as those of RIF in the treatment of drug-susceptible TB,[8,9] few data on the efficacy of RFB in the treatment of MDR-TB are available.[10,11]

Although the level of cross-resistance between RIF and RFB has been reported to be approximately 90%,[12,13] it is known to be relatively low in South Korea, with as many as 20—30% of patients with RFB-susceptible MDR-TB.[14,15] Thus, RFB might be a successful drug for the treatment of a subset of MDR-TB. However, to date there has not been any study conducted to address this issue in South Korea. Therefore, we retrospectively investigated the role of RFB in the treatment of RFB-susceptible MDR-TB.

Methods

Study subjects

Because drug susceptibility testing (DST) to RFB began in South Korea in 2006, our study subjects were selected from the MDR-TB registry of Asan Medical Center between January 2006 and December 2009. A total of 146 patients were diagnosed with MDR-TB during this period. Among them, 31 (21.2%) had RFB-susceptible TB, of whom 15 were treated with RFB-containing regimens. The baseline clinical characteristics and drug resistance patterns did not differ between the 15 RFB users and the 16 RFB non-users (data not shown). Among these 15 patients, one was excluded based on less than one month of treatment with RFB due to an adverse event (severe myalgia), leaving 14 patients with RFB-susceptible MDR-TB enrolled. The patients' medical records, TB treatment history with regard to World Health Organization (WHO) guidelines, DST results, treatment modality, and outcomes were retrospectively reviewed.

Using a nested case-control design, we selected 42 subjects from patients with MDR-TB whose DST showed resistance to RFB during the same period to be the control group. This ensured both groups would have an identical drug resistance pattern except for RFB.

Definitions of study measures

Classifications of drug resistance pattern

Four groups were defined as follows[5]: (1) XDR-TB was defined as MDR-TB with bacillary resistance to any one of the fluoroquinolones (FQ) and to at least one of three, second-line injectable drugs (SLID, i.e. amikacin, capreomycin, or kanamycin); (2) pre-XDR-TB_{FQ} as MDR-TB resistant to any FQ; (3) pre-XDR-TB_{SLD} as MDR-TB resistant to at least one SLID; and (4) other MDR-TB as MDR-TB not resistant to both FQ and SLID.

Treatment outcomes

Six treatment outcome categories, i.e. cure, treatment completion, treatment failure, transfer out, default, and death were defined.[16] Treatment success was defined as either cure or treatment completion. As recommended by the WHO, all treatment outcomes were based on AFB (acid-fast bacillus) culture results. The duration of adequate treatment was defined as 18 months or more and 12 months or more after culture conversion.

Radiologic severity

Radiographic severity was estimated using the recommendations of the National Tuberculosis Association of the United States.[17]

Drug susceptibility tests

Conventional DST was performed using the absolute concentration method with Lowënstein—Jensen (LJ) media for isoniazid, RIF, ethambutol, pyrazinamide, streptomycin, kanamycin, cycloserine, *p*-aminosalicylic acid, prothionamide, ofloxacin, and moxifloxacin at the Korean Institute of Tuberculosis, South Korea's supranational TB reference laboratory. The critical concentration level of RFB was set at 20 μg/mL, which is a half the value of RIF (40 μg/mL). Growth greater than 1% of the control was regarded as drug resistance.[15]

Statistical analysis

All analyses were performed using SPSS software (version 12.0, SPSS Inc., Chicago, IL, USA). Comparisons between the RFB group and the control group were made using Mann—Whitney tests for continuous variables and χ^2 test or the Fisher's exact test for categorical variables. All tests of significance were two sided; $p < 0.05$ was considered statistically significant.

Results

Characteristics of study subjects

Of the 14 patients in the RFB group, five (35.7%) were defined as having XDR-TB, six (42.9%) with pre-XDR-TB_{FQ}, one (7.1%) with pre-XDR-TB_{SLD}, and two (14.3%) with other MDR-TB. The 42 patients in the control group had the same proportion of drug-resistance pattern as that of the RFB group (Table 1). Baseline characteristics such as age, sex,

Table 1 Drug resistance pattern of 56 patients with MDR-TB.

Drug resistance pattern	RFB group (n = 14)	Control group (n = 42)
XDR-TB	5 (35.7)	15 (35.7)
pre-XDR-TB_{FQ}	6 (42.9)	18 (42.9)
pre-XDR-TB_{SILD}	1 (7.1)	3 (7.1)
Other MDR TB	2 (14.3)	6 (14.3)

Abbreviations: RFB = rifabutin; XDR = extensively drug-resistant; TB = tuberculosis; FQ = fluoroquinolones; SLID = second-line injectable drugs; MDR = multi-drug-resistant.
Values are number (%).

previous history of TB treatment, and radiologic severity were comparable in the two groups. Human immunodeficiency virus (HIV) tests were conducted on five (8.9%) patients with none showing positive results (Table 2). Patients who were not tested for HIV did not have any clinical indications of HIV infection at initiation of treatment or during follow-up. The resistance rates for all anti-TB drugs were similar between the two groups except for RFB (Table 3).

Treatment modalities and drug tolerance

All patients in both groups were treated using individualized regimens on the basis of their DST results and their history of previous TB drug regimen. All 14 patients received 300 mg/day of RFB with a mean duration of RFB treatment of 518.4 (±204.2) days and a median duration of RFB treatment of 537 (range 235−832) days.

All 14 patients in the RFB group tolerated RFB well, without any adverse events. In the case of other drugs, each one patient of two (14.3%) in the RFB group did not tolerate either prothionamide or *p*-aminosalicylic acid, respectively. In the control group eight patients (19.0%) had adverse events to various other drugs:prothionamide (n = 3), *p*-aminosalicylic acid (n = 2), kanamycin (n = 2), and pyrazinamide (n = 1).

Surgical resection of pulmonary lesion was performed on six patients (10.7%) out of a total of 56 patients, without a statistically significant difference between the two groups (Table 4). The median number of total prescribed drugs and drugs active against TB was significantly higher in patients in the RFB group (Table 4). However, when RFB was not counted, no significant differences were found between the two groups. Although the use of linezolid was higher in the RFB group, it did not show a significant difference (Table 4).

Treatment outcomes

Treatment success was achieved in 12 (85.7%) patients in the RFB group: cure in 10 (71.4%) and treatment completion in two (14.3%). The treatment success rate was 52.4% (22/42) in the control group (p = 0.032). Treatment failure was more common in patients of the control group (40.5% vs.

Table 2 Clinical characteristics of 56 patients with MDR-TB.

Characteristics	RFB group (n = 14)	Control group (n = 42)	*p*-value
Age (yr)	44.4 ± 14.2	41.7 ± 15.6	0.438
Sex (M/F)	7/7	19/23	0.757
BMI (Kg/m^2)	19.4 ± 2.9	21.7 ± 4.1	0.175
Underlying diseases			0.333
Diabetes mellitus	1 (7.1)	7 (16.7)	
Malignancy	0	2 (4.8)	
Other[a]	0	3 (7.1)	
Previous history of TB treatment			
History of TB treatment with first-line drugs only	8 (57.1)	26 (61.9)	0.136
History of TB treatment with second-line drugs	5 (35.7)	15 (35.7)	1.000
≥2 previous TB treatments	6 (42.9)	19 (45.2)	0.954
Family history of TB	4 (28.6)	12 (28.6)	1.000
Extrapulmonary TB	0	1 (2.4)	1.000
HIV seropositive (n = 5)	0/1 (0.0)	0/4 (0.0)	1.000
Positive AFB smear at treatment initiation	14 (100)	36 (85.7)	0.319
Radiologic severity			0.314
Minimal	8 (57.1)	27 (64.3)	
Moderately advanced	3 (21.4)	3 (7.1)	
Far advanced	3 (21.4)	12 (28.6)	
Bilateral disease	6 (42.9)	22 (52.4)	0.537
Cavitary disease	4 (28.6)	19 (45.2)	0.355

Abbreviations: RFB = rifabutin; BMI = body mass index; TB = tuberculosis; HIV = human immunodeficiency virus; AFB = acid-fast bacillus.
Values are mean ± SD or number (%).
[a] 'Other' includes hypertension (n = 1), chronic pancreatitis (n = 1), and chronic renal disease (n = 1).

Table 3 Drug resistance rate at treatment initiation.

TB drugs	RFB group (n = 14)	Control group (n = 42)	p-value
Pyrazinamide	11 (78.6)	31 (73.8)	1.000
Ethambutol	11 (78.6)	36 (85.7)	0.676
Streptomycin	4 (28.6)	23 (54.8)	0.126
Kanamycin	6 (42.9)	14 (33.3)	0.520
Capremycin	2 (14.3)	10 (23.8)	0.709
Ofloxacin	11 (78.6)	36 (85.7)	0.676
Moxifloxacin	9 (64.3)	23 (54.8)	0.756
Cycloserine	5 (35.7)	10 (23.8)	0.489
p-aminosalicylic acid	7 (50.0)	21 (50.0)	1.000
Prothionamide	9 (64.3)	17 (40.5)	0.138

Abbreviations: TB = tuberculosis; RFB = rifabutin.
Values are number (%).

14.3%; $p = 0.106$) (Table 5). Of 34 patients who attained treatment success in both groups, no patients experienced relapse during the median 21 months (range 4—49 months) of follow-up.

Discussion

Although current guidelines recommend the limited use of RFB in drug-susceptible TB for patients with acquired immune deficiency syndrome or experienced intolerance to RIF,[6,7] the use of RFB in patients with MDR-TB has not yet been described. Since some patients' MDR-TB was susceptible to RFB, this drug can be used in such cases, as is supported by our findings. Our study supports the hypothesis that RFB seem to be useful in the treatment of MDR-TB as an additional drug in patients who have RFB-susceptible MDR-TB infections.

To date, only a few studies have been conducted to determine the effectiveness of a RFB-containing regimen in MDR-TB.[10,11] Bacteriological conversion was achieved in 34% among 270 patients in a study performed in five nations,[10] and Lee et al. reported that 47% of 43 patients achieved sustained sputum conversion with a RFB-containing regimen in Taiwan.[11] However, as neither study had a control group in order to compare the efficacy of RFB, it was unclear whether the RFB-containing regimen was more effective than conventional therapy that did not use RFB for MDR-TB. Also, RFB susceptibility testing was carried out in only few patients[11] or was not done at all.[10] Conversely, ours is the first study to use a control group to better investigate the efficacy of a RFB-containing regimen. In addition, we accurately classified the patients into two groups on the basis of their DST results to RFB.

Although RFB, spiro-piperidyl-rifamycin derived from rifamycin-S, is mainly used as a substitute for RIF in special situations, the American Thoracic Society guidelines classify RFB as a first-line anti-TB drug.[7] In addition the WHO guidelines recently added RFB to group 1 drugs, the most potent and best-tolerated anti-TB agents.[16] RIF is an essential component of TB treatment and has been referred to as the most important anti-TB agent because of its excellent sterilizing capacity.[18] Considering that RFB is more active than RIF against slow-growing mycobacteria, including *Mycobacterium tuberculosis*,[19,20] and that RFB has a similar potency to RIF for the treatment of drug-susceptible TB,[9,21] the promising outcome we observed in the RFB group is most likely related to the outstanding potency of RFB against *M. tuberculosis*. In addition, most patients tolerated RFB well in our study. If we had included the single patient who had been excluded because of less than one-month treatment with RFB in the RFB group, the treatment success rate would be 86.7% (13/15) rather than 85.7% (12/14) in the RFB group.

Even though the median number of total prescribed drugs and active drugs was significantly higher in the RFB group, after excluding RFB, there was no significant difference between the two groups in terms of the number of total and active drugs. This suggests that the addition of RFB may be the cause of the improved outcome in the RFB group. Linezolid is classified as a group 5 drug by the WHO guidelines,[16] and Yew et al. reported its excellent efficacy in the treatment of MDR-TB and XDR-TB.[22] The rate of linezolid use did not differ between the two groups in our study and 10 patients in the RFB group achieved treatment success without linezolid treatment, suggesting that treatment success is unrelated to the use of linezolid.

We randomly chose age, sex, and drug resistance pattern-matched control subjects in order to compare the treatment outcomes between the treatment and control groups. The treatment outcome in the control group was similar to others reported in South Korea.[5,23,24] XDR-TB has proven much more difficult to treat making the drug selection for XDR-TB is extremely difficult.[16] While all five patients with XDR-TB in the RFB group achieved treatment success, only three of the 15 patients with XDR-TB in the

Table 4 Treatment modalities of 56 patients with MDR-TB.

Treatment modalities	RFB group (n = 14)	Control group (n = 42)	p-value
No. of total TB drugs used	6 (5—8)	5 (4—8)	0.039
No. of drugs active against TB	4 (2—6)	2 (0—5)	0.029
No. of patients, treated with linezolid	4 (28.6)	8 (19.0)	0.477
No. of patients, surgical resection	2 (14.3)	4 (9.5)	0.633

Abbreviations: RFB = rifabutin; TB = tuberculosis.
Values are median (range) or number (%).

Table 5 Treatment outcomes of 56 patients with MDR-TB.

Treatment outcomes	RFB group (n = 14)	Control group (n = 42)	p-value
Cure	10 (71.4)	19 (45.2)	0.126
Treatment completion	2 (14.3)	3 (7.1)	0.590
Failure	2 (14.3)	17 (40.5)	0.106
Transfer out	0	1 (2.4)	1.000
Default	0	1 (2.4)	1.000
Death	0	1 (2.4)	1.000
Treatment success	12 (85.7)	22 (52.4)	0.032

Abbreviations: RFB = rifabutin.
Values are number (%).

control group achieved this outcome. This finding suggests that RFB seems to be effective even in the treatment of XDR-TB, if the organisms are susceptible to RFB.

More than 95% of RIF-resistant *M. tuberculosis* have mutations in a hot-spot region of the RNA polymerase β-subunit (*rpoB*) gene.[25,26] The *rpoB* gene mutation is also involved in resistance to RFB.[26] While Uzun et al. reported the high-level cross-resistance (88%) between RIF and RFB,[13] Senol et al. detected 73.1% cross-resistance in Turkey[27] and Chikamatsu et al. identified an overall cross-resistance of 72.7% in Japan.[28] In South Korea, the rate of cross-resistance was 79.6% in one study[14] and 70.5% in another study.[15] The rate of cross-resistance between two drugs varies depending upon the mutation of the *rpoB* gene. The RIF resistance-determining region (RRDR), composed of an 81-bp nucleoside containing codons 507 through 533 within the *rpoB* gene, has been proposed as the most frequently mutated region.[25] Among these codons, mutations at codons 526 and 531 are usually found in isolates of *M. tuberculosis* resistant to both RIF and RFB,[29] while mutations at codons 516 and 522 are associated with resistance to RIF, but only susceptibility to RFB.[30] Our study did not include any investigation into mutations of the RRDR within the *rpoB* gene.

Mutation in the *rpoB* gene eventually leads to structural change of ribonucleic acid (RNA) polymerase. Campbell et al. reported that diverse mutations of the RRDR within the *rpoB* gene are associated with the level of resistance to RIF.[31] That is, if certain mutation can cause significant structural change at a site that is critical to RIF binding, it can cause high-level resistance to RIF. On the other hand, isolates remain susceptible to RIF if mutations make little structural change to the RNA polymerase. Although there have been no studies as to whether mutations at different codons within *rpoB* gene affect binding of the RIF or RFB differently to RNA polymerase owing to the difference of structural change, we think that some mutations can cause structural change to the RNA polymerase which permits binding of only RFB, not RIF. This could be why RFB had a therapeutic effect in a small proportion of patients with MDR-TB with specific *rpoB* gene mutation patterns.

Although our findings suggest favorable treatment outcomes of RFB-containing regimens, some limitations should be considered. The most significant limitation of our study was that it was conducted in a single referral center and with a non-randomized, retrospective design that included a relatively small number of patients. Further studies with a better design and larger sample size are needed to better determine the efficacy of RFB in the treatment of MDR-TB and in order to generalize our findings to a wider population of patients with MDR-TB.

Another limitation was that only about half of patients with RFB-susceptible MDR-TB were treated with RFB, which might induced a selection bias. The main reason why the remaining 16 patients were not treated with RFB was the fact they had already showed a favorable treatment response to initial regimens that did not include RFB at the time of their DST report. Therefore, the 15 RFB-treated subjects could be more prone to a poor treatment response than the 16 patients not treated with RFB, suggesting that selection bias may not factor into the positive treatment success rate in patients with RFB-susceptible MBR-TB.

Finally, in our study, HIV testing was conducted in only five (8.9%) patients. One study reported the HIV prevalence to be less than 0.1% in adults ages 15–49 years in South Korea[32] and Lee et al. showed only 77 (0.05%) of 152,887 patients with TB between 2001 and 2005 were confirmed to have HIV.[33] Since South Korea is a very low HIV-burden country, doctors tend not to identify the possibility of HIV infection in patients with MDR-TB or pulmonary TB. Although the possibility of HIV infection is likely to be low in our study population, the unknown HIV status of the majority of our subjects should also be considered as a significant limitation.

In summary, adding RFB to the treatment of patients with RFB-susceptible MDR-TB resulted in a successful outcome.

Acknowledgments

None.

Conflict of interest statement

No author has a conflict of interest to disclose.

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